D2 142. (Once Amended) The kit of claim 141, wherein said at least one agent is selected from the group consisting of glycerin, trehalose, betaine and [or] DMSO.

Added

REMARKS

Claims 1-126, 132-137 and 141-145 are pending in this application. By this Amendment, claims 138-140 are canceled and claims 133 and 142 are amended. No new matter is added.

The Office Action rejects claims 133 and 142 under 35 U.S.C. 112, second paragraph, for containing asserted informalities. Applicants believe that this rejection is overcome with the above amendments to claims 133 and 142 and reconsideration and withdrawal of the rejection thereof are respectfully requested.

The Office Action rejects claims 1-126, 134-137 and 143-145 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-58 of copending Application No. 09/257,166 in view of Gelfand et al. (U.S. Patent Application No. 5,310,652) and Birch et al. (U.S. Patent Application No. 5,677,152).

As the Office Action notes, the present claims require at least two different polymerases at least one of which has reverse transcriptase activity.

Also as the Office Action notes, the "copending claims", which require two different polymerases, do not teach that at least one of the polymerases has reverse transcriptase activity. However, the Office Action asserts that one of ordinary skill in the

art would have been motivated to modify the methods of the "copending claims" by application towards RNA using a polymerase with reverse transcriptase activity because Gelfand et al. disclosed the advantages of combined reverse-transcription and amplification.

However, it is respectfully noted that the methods of Gelfand et al. "provide a one enzyme procedure ... and replace prior methods requiring more than one enzyme" (column 5, lines 29-32). "Thus, the [Gelfand et al.] invention provides methods which **require only one enzyme** where previous methods required two" (column 6, lines 34-36, emphasis added). Thus, Gelfand et al. clearly teach against a procedure requiring more than one enzyme, such as the two different polymerases of the present claims.

As noted in the U.S. Manual of Patent Examining Procedure Section 2143.01, [if a] "proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." Combining Gelfand, which requires only one enzyme, with the "copending claims...requiring two different polymerases" would clearly render the prior art being modified (either modifying the required Gelfand one enzyme to include two enzymes or modifying the required "copending" two different polymerases to only be include one) unsatisfactory for its intended purpose. Thus, there is no suggestion or motivation to make such a modification.

Birch et al. fail to make up for the deficiencies in the "unsatisfactory for its intended purpose" combination of the "copending claims" and Gelfand et al.

For at least the above reasons, one of ordinary skill would not have been motivated to combine the "copending claims" with Gelfand et al. Thus, it is respectfully

submitted that the presently claimed invention would not have been obvious over the combination of the "copending claims," Gelfand et al. and Birch et al. Reconsideration and withdrawal of the rejection of claims 1-126, 134-137 and 143-145 under the judicially created doctrine of obviousness-type double patenting are respectfully requested.

The Office Action also rejects claims 138-140 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34, 37 and 38 of copending Application No. 09/577,047. Claims 138-140 have been canceled rendering this rejection moot. Thus, reconsideration and withdrawal of the rejection of claims 138-140 under the judicially created doctrine of obviousness-type double patenting are respectfully requested.

The Office Action rejects claims 1-126, 134-137 and 143-145 under 35 U.S.C. 103(a) as being obvious over the combination of Koster et al. (U.S. Patent No. 5,928,906) in view of Gelfand et al. and Birch et al. Similarly, claims 132-133 and 141-142 are rejected under 35 U.S.C. 103(a) as being obvious over the combination of Koster et al. in view of Gelfand et al. and Birch et al. and further in view of Hill (U.S. Patent No. 5,525,492). These rejections are traversed.

As the Office Action notes, Koster et al. disclose methods "requiring two different polymerases..." As the Office Action also notes, the Koster et al. patent does not disclose DNA polymerase-mediated reverse transcription coupled to PCR amplification. However, the Office Action asserts that one of ordinary skill in the art would have been motivated to modify the method of Koster et al. by application towards RNA using a

polymerase with reverse transcriptase activity because Gelfand et al. disclosed the advantages of combined reverse-transcription and amplification.

However, as discussed above for the rejection over the combination including "copending claims", it is respectfully noted that the methods of Gelfand et al. "provide a one enzyme procedure ... and replace prior methods requiring more than one enzyme" (column 5, lines 29-32). "Thus, the [Gelfand et al.] invention provides methods which **require only one enzyme** where previous methods required two" (column 6, lines 34-36, emphasis added). Thus, Gelfand et al. clearly teach against a procedure requiring more than one enzyme, such as the two different polymerases required in the present claims.

As noted in the U.S. Manual of Patent Examining Procedure Section 2143.01, [if a] "proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." Combining Gelfand, which requires only one enzyme, with "Koster...requiring two different polymerases" would clearly render the prior art being modified (either modifying the required Gelfand one enzyme to include two enzymes or modifying the Koster et al. required two different polymerases to only be include one) unsatisfactory for its intended purpose. Thus, there is no suggestion or motivation to make such a modification.

Birch et al., as well as Hill, fail to make up for the deficiencies in the "unsatisfactory for its intended purpose" combination of Koster et al. and Gelfand et al.

For at least the above reasons, one of ordinary skill would not have been motivated to combine Koster et al. with Gelfand et al. Thus, it is respectfully submitted

that the presently claimed invention would not have been obvious over any combination of Koster et al., Gelfand et al., Birch et al. and Hill. Reconsideration and withdrawal of the rejection of claims 1-126, 134-137 and 143-145 and of claims 132-133 and 141-142 under 35 U.S.C. 103(a) are respectfully requested.

The Office Action rejects claims 138-140 under 35 U.S.C. 103(a) as being obvious over the combination of Koster et al. further in view of Birch et al. and Scalice et al. (U.S. Patent No. 5,338,671). Claims 138-140 have been canceled rendering this rejection moot. Thus, reconsideration and withdrawal of the rejection of claims 138-140 under 35 U.S.C. 103(a) are respectfully requested.

Applicants take this opportunity to further note that it was not predicable from the prior art which effects will be seen when using the claimed reversibly inhibited polymerases in sequencing reactions. Moreover, some of these effects can not be explained even today from a hindsight view. It was thus very surprising that the use of inhibiting agent led to clearer and more discrete bands. This conclusion is based on the fact that inhibiting agents were known primarily to reduce primer dimmers in PCR and reduce false, *i.e.* spurious annealing to undesired nucleic acid locations. Standard reactions (*i.e.* reactions as disclosed in Application No. 09/357,166 and Koester et al.) lacking an inhibiting agent have broader signal/sequence peaks which are sometimes difficult to interpret making use of the automated sequence readers often used.

Due to an unknown mechanism the application of the inhibiting agent leads to more needle like peaks which are defined and easy to interpret by the reader. It is unclear how this can be attributed to the known PCR prior art capabilities of inhibiting agents outlined above. Therefore, it was additionally not suggested by the prior art to

utilize using hot-start sequencing reactions in order to achieve needle like peaks, which are defined and easy to interpret by the reader. Thus, a very surprising effect is achieved.

For at least the above reasons, Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,

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Attachment: Marked-Up Copies of Amended Claims

MARKED-UP COPIES OF CLAIMS 133 and 142 SHOWING CHANGES

133. (Once Amended) The method of claim 132, wherein said at least one agent is selected from the group consisting of glycerin, trehalose, betaine and [or] DMSO.

142. (Once Amended) The kit of claim 141, wherein said at least one agent is selected from the group consisting of glycerin, trehalose, betaine and [or] DMSO.